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The Commonwealth of Massachusetts
Executive Office of Human Services
Department of Public Health
150 Tremont Street
Boston 02111

Bailus Waiker, Jr., Ph.D., M.P.H.
Commissioner

Center for Health Promotion and
Environmental Disease Prevention

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TO: Jeffrey Carlson
Chief, Pesticide Bureau

M. Ilyas Bhatti
Director, Division of Water Supply

FROM: Elaine T. Krueger
Acting Director, Division of Environmental Epidemiology and Toxicology

RE: Guidelines for Pesticides in Drinking Water Supplies

DATE: July 23, 1985

Attached for your information are the drinking water guidelines which the Department of Public Health offered to develop and provide to you as described in previous correspondence. This guideline package represents this Department's major contribution to the interagency effort to address the issue of pesticide contamination of ground water used for drinking water. Of course these guidelines could be applied to any drinking water source. In addition to the detailed documentation which is attached, this Division will soon be completing simplified fact sheets which can be used for public information purposes. I will forward these to you by early next week at the latest.

The methodologies used in deriving the guidelines are consistent with those of EPA Office of Drinking Water and the National Academy of Sciences. Briefly, guidelines for the carcinogens were based on determination of risk in the range of one in a million unless this number was less than the limit of detection, in which case the limit of detection is recommended. For guideline development for the pesticides which have a health endpoint of concern which is not cancer, the safety factor approach is taken, since it is assumed that a threshold exists below which effects will not be found.For the noncarcinogens it is assumed that adults consume two liters of contaminated water per day, and that this exposure represents 20% of total exposure, the remainder being from diet. It is also assumed that babies consume one liter of water per day, and that this exposure represents 100% of total exposure, since babies do not consume a similar diet compared to an adult.

Further discussion will need to take place regarding the practical application of these guidelines. For example, ample margins of safety exist in these guidelines, and for concentrations in the range but slightly above the guidelines, it would probably be wise to verify consistently elevated levels before ultimate decision to switch to alternative water supplies is made. This could be accomplished by resampling.

cc: Richard Taupier, EOEA
Gerald Parker, DPH
Kenneth Hagg, DEQE

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Center for Health Promotion and
Environmental Disease Prevention

TO: David M. Gute
Gerald S. Parker

FROM: Elaine T. Krueger

RE: Interim Drinking Water Guidelines for Pesticide Monitoring Program

DATE: July 24, 1985

An interagency groundwater monitoring plan to determine the degree of pesticide contamination in wells used for potable water adjacent to potato and tobacco growing areas has been initiated. The DEQE and DFA will sample and analyze water from both public and private wells. The pesticides being monitored include the following:

aldicarb
ethylene dibromide (EDB)
dinoseb
carbofuran
oxamyl
alachlor
vorlex (constituents are 1,2-dichloropropane - 1,2-D - and 1,3-dichloropropene - 1,3-D)

The Division of Environmental Epidemiology and Toxicology has reviewed the toxicity of these pesticides and developed interim guidelines for them. During the review, toxicologists in Connecticut, Wisconsin, California and New York were consulted for information on their specific actions regarding these chemicals and on general assumptions they use in deriving their guidelines. In addition, staff of three different EPA Offices were consulted for information on the pesticides and methodologies in guideline development currently being used: the Office of Drinking Water (ODW), the Office of Pesticide Programs (OPP), and the Office of Health and Environmental Assessment. Volumes 1 (1977) and 5 (1983) of the National Academy of Sciences' (NAS) Drinking Water and Health were also consulted.

EPA's ODW is currently reviewing a number of these pesticides for which Recommended Maximum Contaminant Levels (RMCLs) will be proposed. RMCLs are non-enforceable health based guidelines which are to be set at levels which would result in no known or anticipated adverse health effects with an adequate margin of safety. RMCLs will be proposed for EDB, 1,2-D, alachlor, aldicarb, and carbofuran. A health advisory, also non-enforceable, is being developed for oxamyl. Neither a health advisory nor an RMCL is being developed for 1,3-D or dinoseb.

In the development of these guidelines, assumptions consistent with EPA's ODW and the NAS were used. These assumptions include the use of safety factors applied to no-observed-effect-levels (NOEL) in animal experiments. The safety factors account for inter- and intraspecies differences and vary depending on the quality of existing data. In addition, the derivation of the drinking water guidelines are generally based on a 70 kg adult who consumes 2 liters of water per day and whose exposure to the chemical via drinking is only 20% of their total exposure. Consideration was also given to a 10 kg child consuming 1 liter of water per day, but whose exposure to the chemical was 100% from the drinking water. For carcinogens, the use of a 10^{-6} excess risk level was generally used. That is, a contaminant level would be set at which one in a million exposed individuals may contract cancer after a lifetime (70 years) of exposure to the chemical in drinking water.

The following interim guidelines are therefore proposed:

Pesticide	Interim Drinking Water Guideline
aldicarb	7 ppb
alachlor	limit of detection (less than 0.15 - 0.25 ppb)
carbofuran	35 ppb
dinoseb	9 ppb
EDB	limit of detection
oxamyl	175 ppb
vorlex: 1,2-D	0.6 ppb
1,3-D	0.2 ppb

cc: Richard Taupier, EOEA
Kenneth Hagg, DEQE
Jeffery Carlson, DFA
M. Ilyas Bhatti, DEQE

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Commissioner

150 Tremont Street
Boston 02111

Center for Health Promotion and
Environmental Disease Prevention

Interim Guidelines for Pesticides in Drinking Water

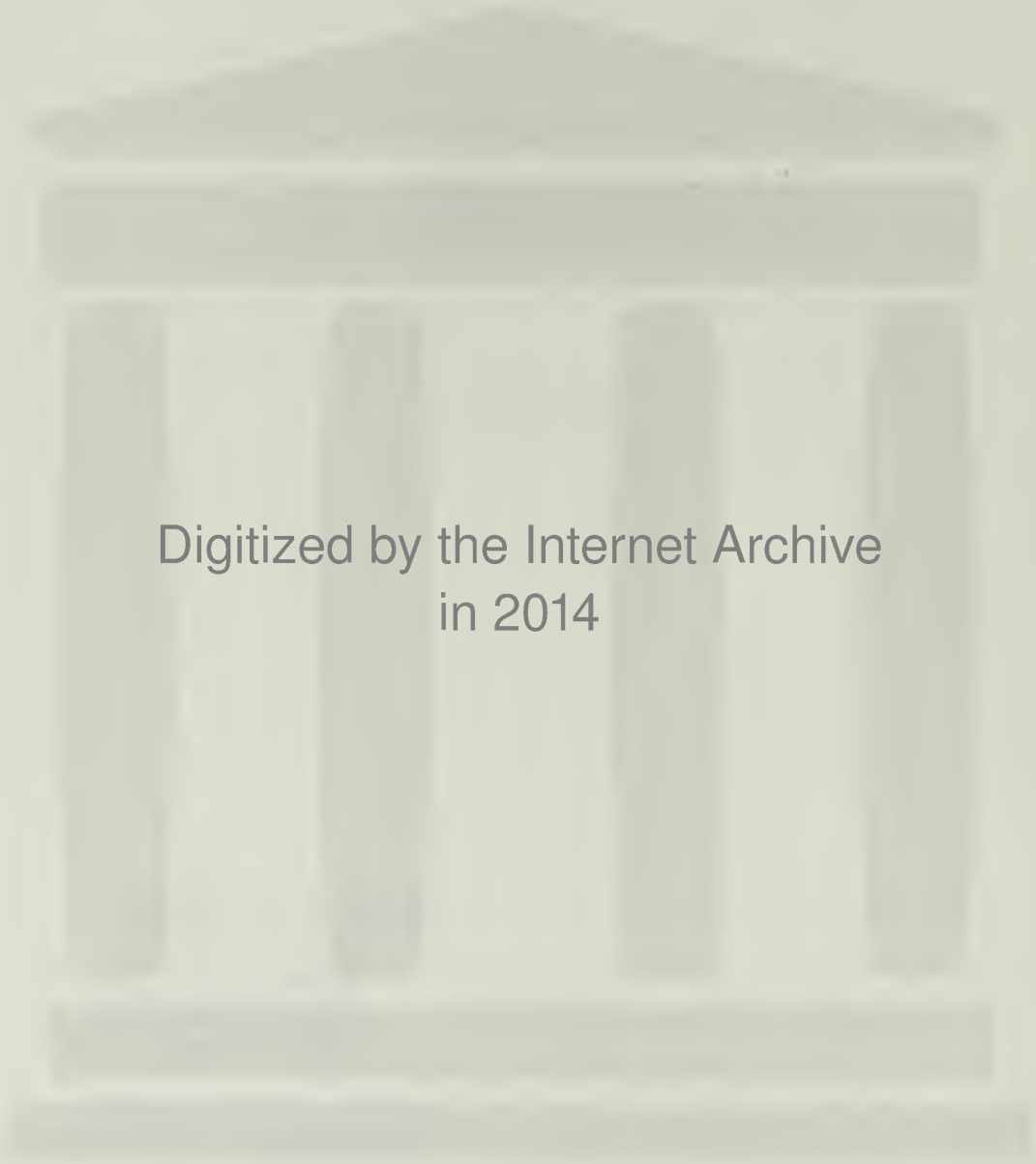
July 1985

Major contributors:

Martha Steele, M.P.H.
Jan Sullivan, M.S.
Elaine Krueger. M.P.H.

Division of Environmental
Epidemiology and Toxicology

Project Nos. T1 - T6



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Alachlor

Background Information

Alachlor is a pesticide manufactured by Monsanto and is known under the trade name Lasso. It has been registered by the EPA since 1969 as a preemergent herbicide for use on broadleaf weeds and grasses and on corn, soybeans, peanuts, and other crops. Corn and soybeans account for 98% of its usage. Food tolerances or maximum permissible residue levels have been set by the FDA for alachlor and certain metabolites of alachlor on raw agricultural products. The EPA Office of Pesticide Programs (OPP) has initiated a Special Review of alachlor (under FIFRA) and has issued a Position Document 1 (PD 1) on it (1). For the general population, exposure to alachlor occurs through residues on treated foods and feed crops and through drinking contaminated water. The EPA began its review because it "determined that the weight of the evidence demonstrates that alachlor is oncogenic to laboratory animals and, in the absence of data on humans, it is prudent to treat alachlor as a probable human carcinogen. Further, certain uses of alachlor are associated with significant exposures, therefore, the Agency has determined that certain uses of alachlor may result in unreasonable adverse effects to man."

The EPA has not taken any regulatory action on alachlor but, in PD 1, the OPP proposed three regulatory options: no change in the registration status, a change in the status, or cancellation. Dr. William Marcus, Chief Toxicologist in EPA's Office of Drinking Water, has reviewed the PD 1 and recommended a fourth option, immediate suspension — to stop the use of alachlor immediately and to remove existing stocks (2). Dr. Marcus based his recommendation on

alachlor being a very potent animal oncogen. In November 1983, OPP imposed new labeling restrictions which are effective during the Special Review period:

(1) use of protective clothing;

(2) tumor hazard warning statement;

(3) water contamination warning statement;

(4) prohibition of aerial application;

(5) prohibition of use on potatoes; and

(6) handling instructions to reduce applicator exposure.

This memorandum summarizes information provided in the PD 1. All of the chronic toxicity studies are unpublished and have been submitted to EPA as part of the registration process. No guidelines or health advisories for alachlor in drinking water presently exist.

Metabolism

Alachlor is rapidly metabolized and excreted in the urine and feces. In a metabolism study with rats, most of the alachlor was eliminated within the first 48 hours, with a half-life of 0.2 to 10.6 hours; the remaining alachlor was eliminated more slowly, with a half-life of 5 to 16 days (1a). Eighty-nine percent of the alachlor was eliminated within 10 days. No information on the metabolites of alachlor (or their toxicity) was provided.

Alachlor is rapidly and easily absorbed through the skin; dermal exposure can be significant for alachlor production workers, pesticide applicators, and some agricultural workers.

Acute Effects

Alachlor is moderately acutely toxic with a rat oral LD-50 of 930 mg/kg(1). Acute exposure to alachlor can produce mild to moderate skin and eye irritation.

Chronic Effects

Noncarcinogenic toxic effects resulting from chronic exposure to alachlor include ocular lesions, hepatotoxicity, renal toxicity, skin sensitization, and maternal and fetotoxic effects. In a two-year feeding study with Long-Evans rats, hepatotoxicity and ocular lesions occurred at all doses tested (14, 42, and 126 mg/kg/day)(1b). The ocular lesions, known as uveal degeneration syndrome (UDS), are significant because they are rare in the Long-Evans rat and in toxicity studies. In another two-year feeding study with the same strain of rats, the initial stage of UDS was noted in the high dose group, 15 mg/kg/day; a no-observed effect level (NOEL) for UDS was noted at 2.5 mg/kg/day (1c). In a six-month feeding study with dogs, hepatotoxic effects were seen at all doses (5, 25, 50, and 75 mg/kg/day) and therefore no NOEL was reported (1d). In a three-generation rat reproduction study, renal toxicity occurred in the second and third generations (1e). No teratogenic effects were noted in a rat teratogenicity study (at three dose levels — 50, 150, and 400 mg/kg/day) but maternal and fetotoxic effects were seen at 150 mg/kg/day (1f).

Carcinogenicity

Alachlor is a potent animal carcinogen in rats and mice. Four chronic feeding studies with alachlor have been conducted; three of them were designed to evaluate its carcinogenic potential. The fourth study, of alachlor-induced UDS, provides additional, qualitative information on alachlor as a carcinogen.

In an eighteen-month feeding study by Daly et al. with CD-1 mice, a statistically significant increased incidence of lung tumors was seen in the female mice at the highest dose (260 mg/kg/day) (1g). The technical alachlor fed to the mice contained epichlorohydrin (ECH; a known carcinogen) as a stabilizer for the first half of the study. While it is possible that the lung cancers could have been ECH-related, a second feeding study by Stout et al. (1983a) demonstrated an alachlor-related carcinogenic effect independent of ECH.

In the Stout et al. (1983a) study, three treatment groups of 50 male and 50 female Long-Evans rats were fed 0.5, 2.5, or 15 mg/kg/day of alachlor (free of ECH). Statistically significant increases were seen in nasal turbinate tumors in both sexes and in thyroid tumors in the male rats (1c). Although not statistically significant, a rare stomach tumor thought to be biologically significant was reported in several dosed rats. Also, a type of brain tumor rare in the particular species tested was seen in several treated animals.

The third chronic feeding study by Daly et al. (1981b) was also with Long Evans rats, 50 per sex at dose levels of 0, 14, 42, and 126 mg/kg/day. These findings included dose-related nasal turbinate tumors (significantly higher in incidence in the treated vs. control groups) in both sexes for the mid and high doses; a statistically significant increase in incidence of stomach

tumors in both sexes for the high dose; and, a statistically significant increase in thyroid tumors in male rats for the high dose (1h). In this bioassay, ECH was present for one year as a stabililzer.

The fourth study of UDS by Stout et al. (1983b) showed an increased incidence of nasal turbinate tumors in rats that were exposed for only five to six months (1i). In this study, Long-Evans rats (50 per sex per group) were fed 0.5, 2.5, 15 or 126 mg/kg/day. According to EPA, this "suggests that partial lifetime exposure (approximately 1/4 of the lifespan of the animals) can result in a similar tumor incidence as a lifetime" (1, p.13).

Below is a summary of the statistically significant carcinogenic responses seen in chronic feeding studies with alachlor (1):

Mouse	Rat
Lung -- at one dose; F	Nasal turbinates -- at three doses; MF*
	Stomach -- at one dose, MF*
	Thyroid -- at one dose, M*

* Seen in more than one study.

No human studies investigating the carcinogenic potential of alachlor have been carried out. Therefore, using IARC's classification scheme for carcinogenicity, alachlor would be a category 2B substance, a probable human carcinogen. Substances in category 2B show inadequate evidence from human studies but sufficient evidence in animals (tumors produced in multiple species or strains, or in multiple experiments, or to an unusual degree with regard to incidence, site or type of tumor, or age of onset). Alachlor would be classified in Group B (sufficient animal evidence) according to EPA's guidelines for carcinogen identification.

Mutagenicity

Limited data on the potential mutagenicity of alachlor exists. Two negative mutagenicity tests were reported -- an Ames test (with and without metabolic activation) and a rec-assay. One positive hepatocyte DNA repair study in rats indicated that alachlor is weakly genotoxic (1j). The EPA, as part of its Special Review, is requiring that more mutagenicity testing be done on alachlor.

Teratogenicity

In its review, EPA reported on one teratology study in which rats were fed alachlor by gavage at 50, 150, and 400 mg/kg/day (1f). No teratogenic effects were seen at any dose level.

Quantitative Risk Estimates

Drinking Water Risks

EPA performed a quantitative risk assessment using tumor incidence data (specifically, nasal turbinate tumors) from the two-year rat study by Stout et al. (1983a) with alachlor free of ECH. (Essentially all of the tumor incidence data was used to generate various risk estimates. All of the estimates were very close in magnitude. EPA chose this study because the alachlor used was free of ECH.) The linearized multistage model was used to estimate carcinogenic potency ($mg/kg/day^{-1}$). The potency estimates were then used to predict lifetime cancer risks for different levels of exposure: potency ($mg/kg/day^{-1}$) x exposure (mg/kg/day) = upper 95% confidence limit for

lifetime cancer risk. The potency estimates used in calculating risk were: 5 x 10^{-2} for males and 1 x 10^{-2} for females. EPA provided the following risk estimates for exposure to alachlor-contaminated drinking water:

Exposure Level(ppb)	Upper 95% Confidence Limit Estimate of Lifetime Cancer Risk	
	10 Kg Child[1]	60 Kg Adult[2]
0.15	10^{-6}	10^{-7} to 10^{-6}
1.5	10^{-5}	10^{-6} to 10^{-5}
15.0	10^{-4}	10^{-5} to 10^{-4}

[1] Consumes 1 liter per day.
[1] Consumes 2 liters per day.

Dietary Risks

EPA also made quantitative risk estimates for dietary exposures from the consumption of residue-containing foods. (These risk estimates do not include the risks from drinking contaminated water.) Two different methods were used to estimate dietary exposure: one uses EPA's standard food factor system to estimate consumption and assumes that alachlor is present in foods at the tolerance levels; the second method uses EPA's new Tolerance Assessment System (TAS) database to estimate consumption and uses the best available alachlor residue estimates. TAS also can be used to estimate dietary exposure for different population subgroups.

With the exception of non-nursing infants, the upper 95% confidence limit for lifetime cancer risk from the consumption of alachlor-containing foods was 10^{-5} to 10^{-4} for every population subgroup. The highest risk (10^{-4}) was for non-nursing infants whose diets contain a high proportion of soybean products. The risk for non-nursing infants may be an overestimate because it assumes

lifetime exposure. However, dietary risks, in general, may be underestimated because the analytical method currently used to measure alachlor residues does not detect an important plant metabolite of alachlor, 2-ethylaniline.

Exposure Data

Alachlor has been found in groundwater drinking sources in Nebraska, Iowa, Maryland, and Ontario at levels ranging from 0.01 to 16.6 ppb for non-spill contamination. It has also been found in surface water in at least nine states, and in municipal water supplies in Ohio. Average concentrations in surface water are generally less than 10 ppb, but go up to 30 ppb. A peak concentration of 268 ppb due to runoff events has been found. Residues of alachlor have also been found on crops. EPA has estimated dietary exposure to be 0.3 to 0.4 ug/kg/day, depending on whether the best available residue level or the tolerance level is used in the estimation. Assuming alachlor is present at the tolerance level in all treated foods represents the worst case. As stated earlier, dietary exposure may be underestimated because the metabolite 2-ethylaniline is not measured. The limit of detection of the analytical method for alachlor in water is generally below 0.15 and 0.25 ppb.

Environmental Behavior

EPA has stated that "in summary, it can be stated that alachlor has demonstrated a potential to leach ... alachlor has been found in wells, and the causes of these findings have ranged from accidental spills to seepage through sinkholes to infiltration through soil from normal agricultural use." Alachlor has been reported to have a low mobility on silty clay loam soil and moderate mobility on sandy and silt loam soils (3). Alachlor can be degraded

in soil; microbial degradation occurs more rapidly under aerobic conditions than anerobic. The average persistence of alachlor in soils is 6 to 10 weeks, depending on soil type and climatic conditions (4). No significant photodecomposition or aqueous degradation occurs (3,4).

Recommended Guideline

On the basis of alachlor's demonstrated carcinogenicity and EPA's quantitative risk assessment, it is recommended that an interim drinking water guideline for alachlor be set at the lowest possible limit of detection. The EPA has stated that this limit is generally below 0.15 and 0.25 ppb. The lifetime risk for a 10 kg child who consumes one liter per day of drinking water containing 0.15 ppb of alachlor is approximately 10^{-6}. This risk estimate does not include the risk from dietary exposure to residue-containing foods. Likewise, a 60 kg adult consuming two liters per day of water containing the same level of alachlor faces a risk estimated at 10^{-7} to 10^{-6}; this risk does not include dietary risks. EPA has estimated the lifetime cancer risk from the consumption of alachlor-containing foods to be 10^{-5} to 10^{-4} for adults and children. Due to these high dietary and drinking water risks, it is imperative to reduce exposure to the lowest possible level.

Project No. T1

References

1. U.S Environmental Protection Agency. Alachlor - Position Document 1. Office of Pesticide Programs. December 31, 1984.

Unpublished studies cited by EPA include the following:

a. Monsanto Co. (1983a) Rat Metabolism Study. MSL-3198, R.D. 493. Part I and II. Unpublished study received Oct. 1983 under EPA Reg. No. 524-316; prepared by Monsanto Agricultural Products Co., submitted by Monsanto Co., Washington, D.C.; CDL: 251543 and 251544.

b. Monsanto Co. (1982) Environmental Fate of Microencapsulated Alachlor: Vol I & II. Unpublished study received May 26, 1982 under EPA Reg. No. 524-344, prepared by Monsanto Agricultural Products Co., submitted by Monsanto Co., Washington, D.C., CDL: 070841.

c. Stout, L.D., et al (1983a) A Chronic Study of Alachlor Administered in Feed to Long-Evans Rats. EHL #800218, Project #ML-80-186, Report MSL-3282/3284. Vol I & II. Unpublished study received Feb. 28, 1984 under EPA Reg. No. 524-316, prepared by Monsanto Environmental Health Laboratory (EHL) submitted by Monsanto Co., Washington, D.C., CDL: 252496-7.

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e. Schroeder, R.D., G.K. Hogan, M.E. Smock, et al (1981) A Three-Generation Reproduction Study in Rats with Alachlor: Project No. 77-2066. Final Rept. Unpublished study received July 10, 1981 under EPA Reg. No. 524-285; prepared by Bio/Dynamics, Inc., submitted by Monsanto Co., Washington, D.C.; CDL: 070177-A.

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h. Daly, I.W., J.B. McCandless, H. Jonassen, et al (1981b) A Chronic Feeding Study of Alachlor in Rats, Project No. 77-2065. Final Report. Unpublished study received Jan. 5, 1982 under EPA Reg. No. 524-285, prepared by Bio/dynamics, Inc., submitted by Monsanto Co., Washington, D.C., CDL: 070586-A, 070587, 8, 9, & 90.

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2. Memorandum - U.S. Environmental Protection Agency, Office of Drinking Water. From William L. Marcus, Chief Toxicologist to Joseph A. Cotruvo, Director, Criteria and Standards Division. December 6, 1984.

3. U.S. Food and Drug Administration. Surveillance Index Document - Alachlor. October 31, 1983.

4. Weed Science Society of America. Herbicide Handbook - Fifth Edition. 1983.

Aldicarb

Background Information

Aldicarb is an insecticide manufactured by Union Carbide and sold under the trade name TEMIK. It provides effective control against the Colorado potato beetle and the golden nematode. The advantage of TEMIK over other insecticides used previously was that it was a systemic insecticide (i.e., absorbed by the roots and moved by sap up to the stems and leaves of the plant) applied at planting.

Metabolism

Aldicarb is a carbamate, a group of chemicals that inhibit cholinesterases, which are enzymes involved in transmitting nerve impulses. Symptoms of carbamate poisoning include perspiration, salivation, muscular weakness, nausea, constriction of pupils, and chest tightness. Unlike the organophosphates, the inhibition of cholinesterases by the carbamates is rapidly reversible. Complete recovery to normal levels is typically about six hours.

Aldicarb is rapidly absorbed by all likely routes of exposure: gastrointestinal, dermal, and inhalation. Its two major metabolites are aldicarb sulfoxide and aldicarb sulfone. The sulfoxide is a slightly more potent cholinesterase inhibitor than the parent compound, while the sulfone is less toxic.

Animal Toxicity

Aldicarb is highly acutely toxic. THe rat oral LD50 is approximately 1 mg/kg. Aldicarb sulfoxide has a similar LD50, and the LD50 of aldicarb sulfone is about 20 mg/kg.

A key study was a six month feeding study in rats with aldicarb sulfoxide. A no-observed-effect-level (NOEL) of 0.125 mg/kg was reported. The only effect noted at higher doses was cholinesterase inhibition (1).

At least five other studies have evaluated the effects of aldicarb after long-term exposures (2,3,4,5,6). Species tested included rats, mice, and dogs. All were feeding studies, ranging from 18 to 24 months in duration. Parameters reviewed included mortality, neoplasm incidence, cholinesterase activity, and other histopathology. The highest dose tested in mice was 0.7 mg/kg/day (6). The mortality rate of this group was significantly greater than one control group,but no other effects were noted.

To date, aldicarb has not been shown to be carcinogenic. All the long term studies mentioned above were designed to evaluate the carcinogenic potential of aldicarb. In addition, the National Cancer Institute (NCI) did a bioassay with aldicarb and found no increase in tumors in either rats or mice (7). The bioassay has been criticized for not using maximum tolerated doses, since the highest dose level given (0.3 mg/kg) did not affect weight gain or mortality. The FIFRA Scientific Advisory Panel (8), however, concluded that the "carcinogenicity of aldicarb has been adequately tested, and the Panel is of the opinion that at the doses tested it does not produce carcinogenic effects". While not all the tests followed the current accepted protocol

(particularly the two earlier rat studies where groups of 20 animals per dose level were tested), a number of expert groups (ODW, FIFRA, NCI, FAO/WHO) have all concluded that aldicarb has not been shown to be carcinogenic.

Aldicarb has not been shown to be teratogenic nor to cause adverse reproductive effects. A three generation reproductive study where aldicarb was given in the diet to rats produced negative results (9). No adverse effects were seen in fertility, gestation, viability, or lactation. In rats, the highest dose level has been 1 mg/kg, and there were no significant effects on fertility, viability, gestation, lactation, or congenital malformations (4). There are reports of decreased cholinesterase activity in fetal tissues in rats at a maternal dose as low as 0.001 mg/kg (administered on day 18 of gestation), although the depression was not associated with any toxic signs or resulting pathology (10). EPA's Office of Drinking Water, concerned about this effect has asked its Office of Research and Development to repeat this study to clarify aldicarb's effect on the fetus.

Mutagenic tests have also been negative. A series of Ames tests were negative (11), as was a dominant lethal test (9) and tests with a Saccharomyces D-3 system (12).

Human Studies

There has been only one human clinical study (13). The study involved 12 male volunteers, divided into three groups of four each. A single acute dose was given. Concentrations were 0.025, 0.05 and 0.1 mg/kg. Clinical symptoms, such as weakness of legs and arms, pin-point pupils, sweating, salivation, nausea, and vomiting, were seen in the group with 0.1 mg/kg, but not in the others. All groups showed some cholinesterase depression. In the lowest dose

group, the decrease was as high as 53% of one hour pre-exposure values. In the 0.05 group, values dropped to 43% of the control values. In the highest dose group, it dropped to as low as 35% of control values. At six hours, all three groups were at 90% of control values. The significance of the cholinesterase depressions seen here is not known.

Exposure Data

Aldicarb residues have been found in groundwater in New York, Wisconsin, Maine, Florida, Arizona, Virginia and Massachusetts. Contamination of groundwater in most instances was generally the result of a combination of environmental factors that led to more leaching and greater persistence of aldicarb residues than expected.

Tolerances in foods have been established for aldicarb, and some residues in foods, such as potatoes, have been found.

Environmental Behavior

Aldicarb hydrolyzes slowly under basic conditions. It has been found to leach in soils, even soils with a high organic content. Leaching will occur more easily in sandy and acidic soils, moderate to heavy rainfall, and soil temperatures below 50°F. Due to its potential to leach to groundwater and its persistence in the water, label changes have been instituted for TEMIK to decrease such leaching.

Other Guidelines

The FAO/WHO and the Office of Pesticide Programs (OPP) of EPA both use an NOEL of 0.125 mg/kg, as derived from the six month study with aldicarb sulfoxide. ODW uses two long-term studies, one in rats and one in dogs, as the basis of its NOEL of 0.1 mg/kg. While the NOELs are essentially the same, all three groups apply a different margin of safety to derive an Acceptable Daily Intake (ADI). OPP applies a margin of safety of 40 for an ADI of 0.003 mg/kg, while ODW applies a margin of safety of 100 for an ADI of 0.001 mg/kg. The ODW applies a margin of safety of 100 to be consistent with the NAS Drinking Water and Health (1977) guidelines which state that a margin of safety of 100 should be applied when good chronic or acute toxicity data are available for one or more species, but where good chronic humans exposure data are not available . In addition, ODW stated that the population may also be exposed to aldicarb residues from other sources, primarily food, and be exposed to other cholinesterase inhibitors. Thus, a margin of safety of 10 was felt to be insufficient, while 100 did provide sufficient protection.

Until 1983, FAO/WHO had an ADI of 0.001 mg/kg. It now recommends an ADI of 0.005 mg/kg, or a margin of safety of 25. Details of the reasons for the change are not yet published. According to Dr. Bruce Jaeger of EPA's OPP, the change was made because:

- cholinesterase inhibition by carbamates is rapidly reversible;
- in 1982, Union Carbide did an experiment where a 1:1 mix of aldicarb sulfoxide and aldicarb sulfone (a mix which Union Carbide contends is normally found in drinking water) was given in drinking water to rats for 28 days, and an NOEL of 0.47 mg/kg was observed;

- in the human study, the dose was one acute oral dose, rather than a dose spread out over 24 hours; thus, the peak cholinesterase depression in the human experiment was greater than it would have been if the dose had been spread out over time.

EPA is currently trying to resolve the difference between its Offices of Pesticide Programs and Drinking Water.

In its draft health advisory for aldicarb in 1982, the ODW, given an ADI, applied the following assumptions to derive a drinking water guideline.

10 kg child consumes 1 liter water/day
ADI = 0.001 mg/kg
10 kg child allowed 0.010 mg total dose
(or 10 ug)
Thus, 10 ug/liter water allowed per day or
10 ppb water concentration

The New York Health Department concurs with the ADI of 0.001 mg/kg. Their guideline is 7 ppb, since they use a different calculation to derive water concentrations. That is, a 70 kg adult drinks 2 liters of water per day, and water is considered the source of 20% of the total aldicarb intake per day (other sources include aldicarb in food, for example). New York's guideline is consistent with the NAS Drinking Water and Health guideline. NAS also used an ADI of 0.001 mg/kg derived from two year studies in rats and dogs, and an uncertainty factor of 100.

Recommended Guideline

In January 1984, the DPH recommended a guideline of 10 ppb. In order to be consistent with the methodology currently being used, the DPH recommends that a 7 ppb guideline be adopted. This guideline uses the same ADI adopted by the DPH in 1984, but assumes a 70 kg adult whose exposure to aldicarb via drinking water is 20% of his total exposure.

The guideline is therefore derived as follows:

$$0.001 \text{ mg/kg} \quad \frac{(70 \text{ kg})\ (0.2)}{(2 \text{ liters/day})} = 7 \text{ ug/l or } 7 \text{ ppb}$$

Considerable uncertainty remains regarding the significance of cholinesterase depression. Because of this uncertainty, and the lack of more extensive human data, especially chronic data, it is recommended that a margin of safety of 100 be applied to the animal NOEL of 0.125 mg/kg. The recommendation of 7 ppb in drinking water provides an adequate margin of safety to protect the public health.

Project No. T2

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Carbofuran

Background Information

Carbofuran is a carbamate pesticide used on crops and soil to control insects, nematodes, and mites. It is manufactured by the FMC Corporation and is also marketed by the Chemagro Division of the Mobay Chemical Corporation. Carbofuran was introduced in 1967 under the trade name of Furadan. It is used on crops such as corn (its single highest use), potatoes, rice, strawberries, peppers, peanuts, alfalfa, and tobacco.

The EPA Office of Drinking Water (ODW) has issued a 10-day and chronic SNARL (suggested no-adverse-response level) for carbofuran; these SNARLs are health advisories which are not enforceable. The ODW will be proposing a RMCL (recommended maximum contaminant level) for carbofuran within the next few months; the MCL, when it is finally issued, will be a national, enforceable standard.

Metabolism

Carbofuran is a potent, reversible cholinesterase inhibitor; that is, it interferes with nerve transmission by inhibition of the enzyme acetylcholinesterase. Carbofuran is readily and completely absorbed when ingested by mice and rats. It is also rapidly metabolized and excreted from the body. In one rat study with radioactive-labeled carbofuran, 95% of the administered carbofuran was excreted in the urine or bile within 48 hours (1). The principal metabolites of carbofuran (in mammals and plants) are 3-hydroxycarbofuran, 3-ketocarbofuran, and carbofuran phenol; these metabolites also inhibit cholinesterase (2).

Acute Effects

Carbofuran is extremely acutely toxic with a rat oral LD-50 ranging from 4 to 25 mg/kg (3). Symptoms of carbofuran poisoning include malaise, sweating, light headedness, nausea, blurred vision, excessive salivation, and vomiting (4). One report on five cases of carbofuran poisoning noted that the above effects were short-lived and that recovery was complete after the administration of atropine (5).

Chronic Effects

Two review of the effects of chronic exposure to carbofuran have been published, one by the National Academy of Sciences (NAS) Safe Drinking Water Committee and one by the Food and Agricultural Organization/ World Health Organization (FAO/WHO) expert panel on pesticide residues in food. The studies that the FAO/WHO expert panel and the EPA relied upon for identifying a no-effect level (NOEL) were conducted by consultants for the FMC Corporation at the request of the EPA and FAO/WHO. These studies are unpublished. The NAS review relied solely on published data.

Brain cholinesterase activity is considered to be the most sensitive indicator of exposure to carbofuran, compared to red blood cell (RBC) or plasma enzyme levels (2). These two chronic feeding studies in mice and rats formed the basis for the FAO/WHO ADI (acceptable daily intake) which is discussed below (6):

- Mice (100 males and 100 females per group) were fed carbofuran at dosages of 0, 20, 125, or 500 ppm for two years. Although

designed primarily to evaluate carcinogenic potential, various biochemical and hematologic parameters were also measured. A no-effect level for brain cholinesterase depression was noted at 20 ppm in the diet, which is equivalent to 2.5 mg/kg bw/day.

- Rats (90 males and 90 females per group) were fed carbofuran at dosages of 0, 10, 20, or 100 ppm for two years. Neoplastic, hematologic, and biochemical effects were evaluated as well as mortality, overt toxicity, and behavior. A no-effect level for cholinesterase depression (brain, RBC, and plasma) was reported at 20 ppm in the diet, or 1.0 mg/kg bw/day.

On the basis of data from two unpublished studies, the EPA ODW and Office of Pesticide Programs (OPP) have established an ADI for carbofuran of 0.005 mg/kg bw/day (11). The studies are:

- A one-year dog feeding study in which an NOEL of 0.5 mg/kg bw/day was noted; at higher dose levels, cholinesterase inhibition was seen.
- A two-year rat feeding study in which an NOEL of 1.0 mg/kg bw/day was observed.

A safety factor of 200 was applied to the NOEL derived from the rat study (compared to 100 for the dog study). This was done because of evidence from a human study (at FMC Corporation) with nine males who were given a single dose of carbofuran; the NOEL observed in this study was 0.05 mg/kg bw/day. Because humans appear to be more sensitive to carbofuran than rats (for cholinesterase inhibition), EPA applied a safety factor of 200 to the NOEL observed in the rat study.

Carcinogenicity

The same chronic feeding studies used to establish the FAO/WHO ADI for carbofuran were designed to evaluate its carcinogenic potential (6). In both mice and rats, no significant difference was seen (upon gross and histologic examination) in tumor incidence between the dosed animals and the controls. The duration of exposure was two years. The maximum doses given (100 ppm for rats, 500 ppm for mice) appear to represent the maximum tolerated dose (MTD) because slight decreases in body weight were seen at these levels while excessive mortality and overt toxicity were not.

Mutagenicity

Carbofuran was found to be nonmutagenic in several short-term tests, including the Ames test, a host-mediated hamster cell assay, three bacterial test systems, and a yeast test system. Although chromosomal effects were seen in one plant assay, NAS concluded that no evidence exists to suggest that the DNA damage was directly involved in producing the effects (3).

Teratogenicity

Two teratogenicity studies of carbofuran were conducted at the request of the FAO/WHO expert panel. Both are unpublished but were reviewed in Pesticide Residues in Food - 1980 (6). Groups of 24 mated female rats were fed 0, 0.1, 0.3, or 1.0 mg/kg bw/day of carbofuran during organogenesis (days 6 to 15 of pregnancy). Groups of 17 pregnant rabbits were fed 0, 0.2, 0.6, or 2.0 mg/kg bw/day during organogenesis (days 6 to 18 of gestation). The animals were sacrificed at the end of gestation and examined for soft tissue and skeletal abnormalities. No evidence of teratogenic effects were seen. Increased mortality and cholinergic poisoning at the high dose level in both species prevented evaluation at that level.

A three-generation reproduction study was conducted with rats (10 male and 20 female rats per group; 12 male and 24 females per group were used in the third generation) who were fed 0, 20, or 100 ppm of carbofuran (6). No treatment-related effects (on fertility, gestation, lactation, or viability) were noted at 20 ppm; this level was reported as the dietary level that would induce no effect on reproduction. Reduced body weight was seen throughout the study at the high dose level.

Exposure Data

Exposure to carbofuran can occur through the consumption of crops and feed containing carbofuran residues and through drinking water contaminated with carbofuran. Limited food monitoring data exists. The FDA estimated in 1980 that the major dietary exposures result from residues on corn, alfalfa (meat and dairy feed), rice, and potatoes. If residues were found to be at the tolerance levels on all crops for which tolerances exist, then approximately

0.232 mg/day/1.5 kg diet of carbofuran would be ingested by a 60 kg individual. This is equivalent to 0.00377 mg/kg bw (7). Carbofuran has been detected in Wisconsin wells at levels of 1 to 270 ppb (8).

Environmental Behavior

Carbofuran has a half-life in soil of 30 to 60 days (3). It is relatively soluble in water and able to move in soil.

Existing Guidelines

Below is a summary of existing guidelines for carbofuran, and the NOELs which formed the basis for the guidelines:

Guideline	NOEL (mg/kg bw/day)	Basis for NOEL	Safety Factor
FAO/WHO ADI of 0.01 mg/kg bw/day	1.0	2-yr. rat feeding study	100
EPA OPP ADI of 0.005 mg/kg bw/day	0.5	1-yr. dog feeding study	100
	1.0	2-yr. rat feeding study	200
EPA ODW Health Advisory (1) chronic SNARL of 50 ppb 10-day SNARL of 0.1 ppm	0.5	same as above	100
NY drinking water guideline of 15 ppb	0.05	human cholinesterase study	10

(1) Wisconsin has adopted EPA's health advisory as a groundwater standard. EPA's 10-day SNARL is based on the EPA OPP tolerance level in milk.

Recommended Guideline

Using the ADI of 0.005 mg/kg bw/day established by EPA Office of Drinking Water and Office of Pesticide Programs, a recommended interim guideline can be established. (As stated earlier, the EPA will be proposing a RMCL for carbofuran within the next few months.)

assumptions made: NOEL of 0.5 mg/kg bw/day
20% of intake from water
70 kg individual consumes 2 liters/day
uncertainty factor of 100 following
NAS guidelines

$$\frac{0.5 \text{ mg/kg} \times .20 \times 70 \text{ kg}}{2 \text{ liters} \times 100} = 0.035 \text{ mg/liter} = 35 \text{ ppb}$$

The above calculation can be made for a 10 kg child whose total exposure is assumed to be through drinking water. The guideline becomes 50 ppb. Therefore, the recommended guideline of 35 ppb also protects a child consuming carbofuran in drinking water.

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Dinoseb

Background Information

Dinoseb (2-sec-butyl-4,6-dinitrophenol) is an herbicide and insecticide that has been used since 1945. It is an organonitro compound. Its common names include DNBP, DNOSBP, and DNSBP; its trade names include Dow General Weed Killer, Sinox General, Cladon, and Preemerge. It is produced in the US by Dow Chemical Company, Drexel Chemical Company, and Vertax Chemical Corporation. Dinoseb's primary use is the control of weeds on various agricultural field crops, fruits, vegetables, and nuts. Tolerances have been established for many foods. Exposure to dinoseb occurs through the ingestion of dinoseb residues on food or through drinking dinoseb-contaminated water. Dermal and inhalation exposure is of importance for pesticide and agricultural workers. Due to insufficient data, the EPA Office of Pesticide Programs (OPP) has required the registrants for dinoseb to begin several chronic toxicity studies and to collect environmental fate data. The EPA Office of Drinking Water has not evaluated dinoseb. EPA will begin receiving the toxicological data in 1986.

Metabolism

Dinoseb increases metabolic activity through the uncoupling of oxidative phosphorylation and the disruption of ATP synthesis. In extreme cases, exposure to dinoseb can bring about hyperthermia. In ruminants, dinoseb can cause methemoglobinemia and hemolysis (lysing of red blood cells (RBCs)); this occurs when dinoseb is reduced to an amine which may then cause the oxidation of hemoglobin to methemoglobin. (Methemoglobin is not capable of carrying

oxygen in RBCs, which is one of the main functions of hemoglobin.) Dinoseb is readily absorbed into the bloodstream when ingested, inhaled, or absorbed through the skin. Rats fed C-14 labeled dinoseb excreted 40 to 65% of the C-14 in the urine and 30 to 40% in the feces within 72 hours (1). No information on metabolites was provided.

Acute Effects

Dinoseb is extremely acutely toxic. The oral LD-50 in rats ranges from 25 to 40 mg/kg (2). Symptoms of dinoseb poisoning include increased body temperature, sweating, fatigue, thirst, increased respiration, nausea, tachycardia (rapid heart beat), cyanosis, and coma.

Chronic Effects

The National Academy of Sciences (NAS) Safe Drinking Water Committee reported on two rat feeding studies. In a six-month study, rats were fed dinoseb at dosages of 5.6 to 22.7 mg/kg bw/day (3). A no-effect level (NOEL) was reported at 5.6 mg/kg bw/day. Decreased growth and organ weights and elevations in blood urea nitrogen (BUN) were seen at the higher dose levels. In a five-month study, rats were fed dinoseb at 0, 50, 150, 200, 300, 400, and 500 ppm (4). Excessive mortality occurred at 300 and 500 ppm. No NOEL was observed. At the lower doses, various effects including decreased growth, decreased organ weights, and altered enzyme levels were seen. At 200 ppm in the diet, diffuse testicular atrophy occurred. In a 1980 FDA Surveillance Index Document, the results of a 90-day dog study were provided (no reference was given). Dogs were fed dinoseb at dosages of 0, 0.005, 0.01, 0.02, or 0.03

percent of the diet. The number of animals in the study was not reported. At 0.02 and 0.03 percent, growth retardation, increased liver weight, and endocarditis occurred. An NOEL was observed at 0.01 percent of the diet or 4 mg/kg bw/day.

In its proposed tolerance for dinoseb, the EPA referred to several unpublished studies in which NOELS were reported (11):

	NOEL (mg/kg bw/day)	
o 6 month rat feeding study	5	
o 3 month dog feeding study	7.5	
o 3 month dog feeding study	2.5	
o rat teratology study	> 15	for teratogenic effects
	5.0	for fetotoxic effects
o mice teratology study	32	for teratogenic effects

The EPA Office of Pesticide Programs has established a provisional ADI for dinoseb of 0.0013 mg/kg bw/day. A safety factor of 2000 is incorporated into the ADI; this safety factor was chosen because the NOEL was based on a subchronic study (1, 11). This is consistent with existing OPP policy on uncertainty factors. This ADI was based on the NOEL of 2.5 mg/kg bw/day.

Carcinogenicity

NAS reported that dinoseb did not produce a significant increase in tumors in two strains of mice when given the maximumm tolerated dose (MTD) for 18 months (5). However, because only 18 mice per sex per strain were used in the

experiment, it lacks the statistical power that is considered adequate in current bioassays. The EPA is requiring that the registrants for dinoseb conduct an oncogenicity study, the results of which are due in 1988.

Mutagenicity

Limited mutagenicity data exists on dinoseb. Negative results were obtained in two microbial assays -- one viral and one bacterial (with eight different strains of Salmonella). However, no metabolic activation system was used in the assays (6). Positive results (mitotic gene conversion) were reported in one mutagenicity assay with yeast; no metabolic activation system was needed to elicit the response (7). In addition, dinoseb inhibited RNA and protein synthesis in mammalian cells exposed to 350 ug/ml for 30 minutes; the NAS Committee postulated that dinoseb's effect on oxidative phosphorylation and ATP synthesis might have been responsible for the inhibition. In summary, dinoseb has shown positive mutagenic activity in one short-term test, and its effect on protein synthesis (in one test) could be due to its effect on metabolism and not a genotoxic effect. The data are inadequate for evaluation at this time.

Teratogenicity/Reproductive Effects

Dinoseb was administered to pregnant mice at different times during organogenesis (8). When given intraperitoneally or subcutaneously, maternal and embryo toxicity occurred at a dose of 17.7 mg/kg; teratogenic effects (skeletal defects, cleft palate, hydrocephalus, and absence of the adrenal gland) were noted in the surviving embryos. No skeletal or soft tissue

defects occurred when dinoseb was administered orally at 20 or 32 mg/kg/day. Follow-up to the above study showed that the elimination of dinoseb and peak concentration time depends on the route of exposure: (1) elimination was four times faster following oral doses, and (2) peak levels were reached much faster following injection (9). This seems to explain, at least partially, why teratogenic effects were seen following parenteral doses but not oral doses. In this same study, it was shown that dinoseb does not readily cross the placenta; levels in the embryo never exceeded 2.5% of the maternal plasma levels. NAS concluded that "these data indicate that dinoseb is teratogenic to mice after parenteral doses, but teratogenicity was not observed after oral exposures" (2, p.49). Two additional teratogenicity studies of dinoseb were summarized in the FDA Surveillance Document (1). (The number of rats or mice per dose group was not reported.) In one study, rats were administered oral doses of 0, 2.5, 5.0, and 10 mg/kg bw/day during organogenesis (day 6 to 15 of gestation). No anomalies were reported. In the second study, mice were fed oral doses of 0, 20, 32, and 50 mg/kg bw/day of dinoseb on various days of gestation (days 10-12, 14-16, or 8-16). Maternal deaths occurred at the high dose and maternal toxicity was seen at all doses. Embryo toxicity was also observed (dose was not given). No teratogenic effects were noted.

As part of its special review of dinoseb , the EPA is requiring the registrants to conduct a reproduction study (in one species) and a teratogenicity study (in one species other than mice); results from the teratogenicity study are due in mid-1986 and the results from the reproduction study are due in 1988.

Environmental Behavior

Dinoseb is slightly soluble in water. It does not readily hydrolyze and appears to be persistent in water. Dinoseb undergoes microbial degradation in soil. Thirty-four percent of the dinoseb applied to silt loam soil remained after six months. Based on greenhouse studies, the half-life of dinoseb in soil is estimated to be 34 to 111 days (1). Dinoseb is not tightly adsorbed on most soils. It can leach in sandy, porous soil. Under normal conditions, dinoseb is expected to remain in the top foot of soil during the first year of application (what "normal" conditions means was not explained) (10).

Existing Guidelines

The NAS established a chronic SNARL (suggested no-adverse-response level) of 39 ppb, based on the NOEL identified by Spencer et al.(3).

Assumptions made: NOEL of 5.6 mg/kg bw/day
20% of daily intake from water
70 kg individual consumes 2 liters/day
uncertainty factor of 1000 for limited or incomplete chronic toxicity data

$$\frac{5.6 \text{ mg/kg} \times .20 \times 70 \text{ kg}}{2 \text{ liters} \times 1000} = 0.039 \text{ mg/liter (ppm) or } 39 \text{ ppb}$$

Recommended Guideline

Data on dinoseb from chronic feeding studies are lacking. An interim guideline for dinoseb can be established using EPA's provisional ADI of 0.013 mg/kg bw/day:

assumptions made: NOEL of 2.5 mg/kg bw/day
20% of intake from water
70 kg individual consumes 2 liters/day
uncertainty factor of 2000 because of reliance on subchronic data

$$\frac{2.5 \text{ mg/kg} \times .20 \times 70 \text{ kg}}{2 \text{ liters} \times 2000} = 0.009 \text{ mg/liter} = 9 \text{ ppb}$$

If instead an uncertainty factor of 1000 is assumed, which is consistent with NAS guidelines, then a guideline of 18 ppb is calculated. The above calculations can be made for a 10 kg child whose total exposure is assumed to be through drinking water. With an uncertainty factor of 2000 and 1000, the guideline becomes 12.5 and 25 ppb, respectively.

Therefore, the above guideline of 9 ppb can be expected to protect a child consuming dinoseb in drinking water. A 2000-fold uncertainty factor has been chosen because EPA's Office of Pesticide Programs used this uncertainty factor in calculating its provisional ADI; when data from chronic studies become available, this uncertainty factor may be reduced.

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Oxamyl

Background Information

Oxamyl is used as a systemic or contact insecticide, miticide, and nematocide, and has been used on potato crops here in Massachusetts. It is manufactured by DuPont.

All of the studies cited below are unpublished. They were discussed in the Food and Agricultural Organization's (FAO) Pesticide Residues in Food series. In addition, DuPont supplied us with summaries of these studies.

Metabolism

Oxamyl is metabolized in animals by two major pathways, hydrolysis to its oxime and enzymatic conversion to N,N-diethyloxamic acid. The metabolites are all less acutely toxic than the parent compound, with most of them being substantially less toxic (5).

Studies in rats showed 70% of the dose of oxamyl was eliminated in 24 hours. Twenty-two (22%) of the dose was incorporated into skin and hair tissue as metabolic products, with an absence of toxicity indicated (1).

Acute Toxicity

Oxamyl is a carbamate, and is highly acutely toxic. Its rat oral LD 50 is 5.4 mg/kg (RTECs), although an LD50 of 2.5 mg/kg has been reported (5). Acute effects are typical of carbamate poisoning, that is, cholinesterase inhibition that is rapidly reversible. In a 29-day rat feeding study measuring cholinesterase inhibition, an NOEL of 50/mg/kg in the diet was determined

(1a). This translated to approximately a 2.5 mg/kg dose. Another 10-day study on rats was conducted (3). A group of 6 male rats were given oral doses of 2.4 mg/kg oxamyl. Mild clinical symptoms (fasciculations) associated with cholinesterase inhibition were observed from 1 to 4 hours after dosing, and a slight weight loss occurred during the period.

As indicated by studies in rabbits, oxamyl is much less readily absorbed through the skin than by injection. The dermal LD50 in rabbits of oxamyl formulations are at least 2000 mg/kg (6).

Chronic Toxicity

Carcinogenicity studies in rats and mice were negative under test conditions. However, in the rat study, 39% of the males and 43% of the females died prior to the end of 2 years, while in the mouse study, 59% of the males and 61% of the females died prior to the end of 2 years (4). Mutagenicity studies, including the Ames assay, have also been negative (1). A study was with chickens to determine whether oxamyl produced delayed neuropathy was negative (1).

A number of reproductive studies have been done. In one rat study (1b), a maternal NOEL of 50 mg/kg in the diet was determined. At levels higher than this, a decrease in body weight was noted. No effects were seen in the number of implantation sites, resorptions, or on embryonal development. In a 3-generation rat study (1f), litter size, viability, and body weights of weanlings were decreased at 100 and 150 ppm levels in the diet. No effect was seen on fertility and gestation indices. The NOEL was 50 ppm in the diet, or 2.5 mg/kg body weight. On the basis of these studies, oxamyl has not been shown to be teratogenic.

In other chronic studies, a 2-year feeding study in rats found an NOEL of 50 ppm in the diet (1f). At higher doses, a decrease in body weight and organ weight changes were noted. In a 90-day study, the NOEL was again 50 ppm in the diet (1g) with a decreased body weight seen at higher levels.

Only one chronic study in mice has been reported (4) In a two year diet study, a decrease in bodyweight and nutritional performance were noted in the 50 and 75 ppm groups. No mention was made as to whether cholinesterase levels were measured. The NOEL for the study was 25 ppm in the diet, which translates to 3.9 mg/kg dose, assuming a 0.025 kg mouse consuming 0.0039 kg food/day.

Exposure Data

In FDA monitoring for pesticides in foods, oxamyl has not been found since a methodology able to detect oxamyl residue was incorporated in 1980. The total number of examples analyzed for oxamyl was approximately 2000 (7). We do not know of any levels of oxamyl found in drinking or groundwater. The general population is not expected to be subject to dermal or inhalation exposure to oxamyl, although these routes may be significant to pesticide applicators and agricultural workers (5).

Environmental Behavior

Oxamyl's degradation in the environment is highly pH dependent (1). It hydrolyzes readily in water under basic conditions but is stable in water with a pH of 5 or lower. The t1/2 in river water varied between 12 hours and 2 days in a lab study. The rate of decomposition in water will also increase with sunlight, aeration, and higher temperatures.

The t1/2 in soil is also variable, depending on soil type and moisture content. Field studies indicate that oxamyl is not highly mobile in soil, probably due to its rapid degradation. Its t1/2 in soil appears to be approximately 6-8 days (1).

Recommended Guideline

Both the EPA and FAO agree on an NOEL and ADI. The NOEL is 2.5 mg/kg body weight. The FAO based their NOEL on the two year rat feeding study and three generation rat reproduction study (1f), while EPA based it on the rat reproduction study (personal communication, EPA). This same NOEL was evident in a number of studies, including acute, subchronic, and chronic studies, measuring different endpoints, such as cholinesterase inhibition, body and organ weight changes, and maternal toxicity in reproduction studies. One rat study showed mild clinical symptoms at levels of 2.4 mg/kg. Consistent with the NAS guidelines, which are used by EPA's ODW, a margin of safety of 100 is applied because chronic animal data exists, but no human data exists. Thus, the ADI is 0.025 mg/kg, which is the ADI used by EPA (personal communications, EPA ODW). The ADI is then used to derive a drinking water guideline. Possible guidelines based on the 10 kg child and the 70 kg adult are as follows:

For a 10 kg child:

$$0.025 \text{ mg/kg} \quad \frac{10 \text{ kg child}}{1 \text{ liter/day}} = 250 \text{ ug/l}$$

For a 70 kg adult:

$$0.025 \text{ mg/kg} \quad \frac{70 \text{ kg adult} \times 0.2}{2 \text{ liters/day}} = 175 \text{ ug/l}$$

Since the estimate for the adult is more conservative, we recommend a guideline of 175 ug/1 of oxamyl.

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Vorlex

Background Information

Vorlex is used as a soil fumigant to control nematodes, and has been the chief replacement for EDB. Prior to 1983, it consisted of the following ingredients (3):

20% Methyl Isothiocyanate

80% Chlorinated C3 Hydrocarbons - typically containing

50% 1,3-D and 20% 1,2-D

In October 1983, new formulations contained:

20% Methyl Isothiocyanate

40% 1,3-D - which has about 0.5% 1,2-D as a contaminant

20% Inert Ingredients

Due to their chronic toxicity, the ingredients of most concern in Vorlex are 1,2-D (1,2-dichloropropane) and 1,3-D (1,3-dichloropropene).

Metabolism

1,2-D

There is no data on absorption, distribution, biotransformation, or elimination in humans of either 1,2-D or 1, 3-D. In one rat experiment, the authors claimed 80-90% elimination of 1,2-D in the first 24 hours (7). 1,2-D has shown only minimal incorporation into tissues (1).

1,3-D

Excretion of 1,3-D is rapid. In rats, 90% of the dose was eliminated in 96 hours (7). Minimal residue storage occurs in the tissue. Thus, it does not appear to bio-accumulate (5).

Acute Toxicity

1,2-D

The rat oral LD50 for 1,2-D is 2200 mg/kg (RTECs). In acute studies in rats and dogs, effects have been produced on the liver, gastrointestinal tract, and kidney at 350 mg/kg (1). Exposure to 1,2-D is also associated with eye and skin irritation, and headaches (2). Oral doses as low as 8.8 mg/kg in rats interfered with protein formation and lipid metabolism in the liver (1).

The dermal LD50 in rabbits is greater than 8000 mg/kg (RTECs). Thus, it is not as easily absorbed through the skin as by ingestion.

1,3-D

The oral LD50 for rats is 250 mg/kg (RTECs). An inhalation study done in rats showed irritation to eyes and noses of the animals after brief exposure to concentrations greater than 2700 ppm. Severe lung, kidney, and liver damage was also noted. 1,3-D is considered very irritating to the eyes, skin, and mucous membranes, and is more acutely toxic than 1,2-D.

The dermal LD50 in rabbits is 504 mg/kg (RTECs).

Chronic Effects

Carcinogenicity

1, 2-D

In a draft report (10), the NTP classified 1,2-D as having "some evidence of carcinogenicity in two species" (2). This was based on an NCI bioassay where liver adenomas in both female and male mice were significantly elevated. Doses were given by gavage at levels of 62 or 125 mg/kg to male rats, and 125 or 150 mg/kg in female rats and mice. The NTP report also concluded that in female rats, there was "equivocal evidence of

carcinogenicity in that 1,2-dichloropropane caused a marginally increased incidence of adenocarcinomas in the mammary gland concurrent with decreased survival" (2).

Relevant to 1,2-D's potential carcinogenicity is the fact that animal tests with structurally related compounds such as 1,2-dichloroethane, 1,2-dibromoethane, and DBCP showed these compounds are carcinogenic (1). However, 1,2-D has been judged not to be a direct alkylating agent because of its lack of reaction with 4-(p-nitrobenzyl) pyridine (NBP)(8).

1,3-D

An NTP bioassay was done in 1983, and the final report was relesed in May 1985 (18). Telone II (containing about 89% 1.3-D) was tested. Administration was by gavage, with doses of 25 or 50 mg/kg in rats, and 50 or 100 mg/kg in mice. Positive results were seen in the following tissues (6).

forestomach	
squamous cell papillomas	both sexes - rats
squamous cell carcinomas	male rats
papillomas & carcinomas combined	female mice
liver	Male rats
bladder	female mice
lung adenomas	both sexes - mice

The NTP report concluded there was "clear evidence of carcinogenicity" in male rats, "some evidence" in female rats, and "clear evidence" in female mice. Due to reduced survival in the control group, the study in male mice was considered inadequate. There was, however, some indication in the male mice of carcinomas in the bladder, squamous cell papillomas in the fore stomach, and adenomas and carcinomas of the lung (18).

Another study in mice was done with subcutaneous injection of 1,3-D. A significant number of sarcomas at the injection site occurred, but direct application to the skin did not produce any malignancies (17).

Mutagenicity

1,2-D

NTP reported that mutagenic results in the Ames assay are marginal (1). The NTP noted that 1, 2-D caused both sister chromatid exchanges (SCE) and chromosomal aberrations in Chinese hamster ovary cells. "Each test indicates the potential of these chemicals to induced changes in genetic material (1).

1,3-D

1,3-D has reportedly been strongly mutagenic in the Ames assay with and without activation in two strains (4). A later report questioned whether these results may have been due to impurities (13). NTP noted "Nonetheless, Telone II was mutagenic in Salmonella strains in the presence or absence of S9" (18). Another study showed that 1,3-D was a direct acting mutagen (11). 1,3-D has also induced a significant number of SCEs in Chinese hamster ovary cells (14). 1,3-D has been shown to alkylate (12). But the rapid metabolism and elimination of 1,3-D suggest that the effects of such alkylation could be minimized (1).

Reproductive Effects

There is no information for either chemical on these endpoints.

Other Chronic Studies

1,3-D

A 13-week oral administration study was done in rats at dose levels from 1 to 30 mg/kg. An increase in kidney weight in female rats occurred at 30 mg/kg and in males at both 10 and 30 mg/kg (16).

In another experiment, rats were fed 0.1 to 2.5 mg/kg over a 6 month period. There was a permanent increase in lipase activity and changes in several blood serum enzymes (16). Another study reported rats fed 2.2 mg/kg over 30 days exhibited altered excretory functions of the liver. There also appeared to be little body accumulation of the chemical (1a).

In an inhalation study, a number of species were exposed to 1 and 3 ppm for 185 days (15). At 3 ppm (13.6 mg/m^3) in rats, kidney effects were seen in males, and higher liver to body weight ratios were seen in females.

Humans - Occupational Exposure

The California Department of Food and Agriculture warns against excessive exposure to 1,3-D. Such exposure can cause skin and eye irritation, and CNS effects. Other symptoms typical of accidental exposure include nausea, cramps, headaches, rash, and difficulty in breathing.

Findings from three case reports suggested a causal relationship between exposure to 1,3-D and hematological malignancies (9). Two of the cases were of firemen who responded to a chemical spill of 1,3-D. Both were treated for acute symptoms after the spill. Approximately 6 1/2 years later, both men developed histiocytic lymphoma and died within two months of each other. In the third case, leukemia developed in a farmer exposed to 1,3-D during application to the soil.

Quantitative Cancer Risk Assessment

1,2-D

Two quantitative estimates have been done. Dr. Edward Calabrese at the University of Massachusetts performed an analysis for the Connecticut Health Department. According to Dr. Calabrese, the total dose associated with a one in a million risk is 28.7 ug/70 kg person/day, for a lifetime exposure. If one assumes a 2 liter water consumption per day, this would translate to a level in water of 14.3 ug/1, where a 10^{-6} risk would be.

In a draft of the Drinking Water Criteria Document for 1,2-D dated March 1985, EPA calculated the level in drinking water of 1,2-D associated with a 10^{-6} risk which was 0.6 ug/l. EPA used the result of combined liver adenomas and carcinomas in male mice in the 1983 NTP draft report (personal communications, EPA).

1,3-D

EPA's Environmental Criteria and Assessment Office has calculated a potency estimate for EPA's Office of Solid Waste, available in a Health and Environmental Effects Profile for 1,3-D dated June 1985. CAG has reviewed and approved this estimate. The estimate was based on NTP's draft report, where the highest site-specific potency was in female mice, specifically transitional cell carcinomas of the urinary bladder. The potency was 1.74×10^{-1} per mg/kg/d exposure. Assuming a 70 kg adult drinking 2 liters of water, a level in drinking water associated with a lifetime risk of 10^{-6} would be 0.2 ppb, or 0.2 ug/l water.

Other Standards/Guidelines

1,2-D

Connecticut has a guideline of 10 ppb, based on Dr. Calabrese's cancer risk estimate. New York has a guideline of 50 ppb, based only on structural similarities to other chemicals. The EPA ODW has a 10-day health advisory of 100 ppb, based on an NOEL, a margin of safety, a 70 kg person, and 2 liters consumed per day. They also have a tentative long-term SNARL of 10 ppb. These were developed in 1983. California has an informal SNARL of 10 ppb for exposures greater than 10 days, adopted from EPA.

1,3-D

Connecticut has a guideline of 10 ppb. New York, based on structural similarities to other chemicals, such as vinyl chloride, trichloroethylene, and epichlorohydrin, set a guideline of 2 ppb.

Exposure Data

The NAS noted that they had found residues of both 1,3-D and 1,2-D of up to 1 ug/1 in finished water (5). As for 1,2-D, it has been found in Maryland, New York, and California, ranging from 0.2 to 440 ppb. In Connecticut, it has been found up to 45 ppb (personal communication, Connecticut Health Department). New York and California had not detected 1,3-D in their water samples. The amount of these compounds ingested by humans through food is not known (5).

Environmental Behavior

1,2-D

1,2-D appears to undergo minimal degradation in soil, with the major route of dissipation being volatilization (5). It is highly water soluble and has a low rate of hydrolysis. Thus, it is quite persistent in water. It also moves more easily through soils than 1,3-D.

1,3-D

1,3-D can be rapidly hydrolyzed in soils (1). In one study, 1,3-D had a t1/2 of 5.3 months in the soil (2). Volatilization is the most significant mechanism for dispersal (5). It is rapidly hydrolyzed in water (3). Unlike 1,2-D, 1,3-D is not persistent and appears to undergo rapid environmental transformation (1).

Recommended Guideline

Since both 1,2-D and 1,3-D have produced cancers in laboratory animals, a guideline should be set based on this endpoint. CAG has estimated that a 10^{-6} excess risk is posed by exposure to 0.6 ppb 1,2-D in drinking water. EPA's Criteria and Assessment Office calculated a 10^{-6} risk corresponded to 0.2 ppb of 1,3-D in drinking water. We therefore propose that Massachusetts adopt these levels in drinking water, as a 10^{-6} risk level is commonly used for regulatory purposes. Thus, the guidelines are:

1,2-D	0.6 ppb
1,3-D	0.2 ppb

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The Commonwealth of Massachusetts
Executive Office of Human Services
Department of Public Health
150 Tremont Street
Boston 02111

Bailus Walker, Jr., Ph.D., M.P.H.
COMMISSIONER

April 26, 1984

Anthony D. Cortese, Sc.D.
Commissioner
Department of Environmental Quality Engineering
One Winter Street
Boston, Massachusetts 02108

Dear Commissioner Cortese:

Thank you for the opportunity to review the proposed drinking water guidelines for EDB.

Summary of Conclusions and Recommendations

Our conclusion, having reviewed the EDB literature in depth over the last few months, is that EDB is a potent carcinogen, mutagen and reproductive toxicant which poses small but definite risks to human health at very low concentrations in drinking water. Quantitative risk assessment estimates confirm this. We believe that exposure to EDB should be minimized or eliminated to the extent feasible. We, therefore, recommend that:

1. for concentrations less than or equal to 0.02 ppb, no limitations should be placed on consumption;
2. for concentrations between 0.02 and 0.10 ppb, an alternative water source should be sought as expeditiously as is technologically and economically feasible but in no case longer than two years;
3. for concentrations above 0.10 ppb, the water supply should be closed, provided the results have been confirmed and are consistent.

In addition, this Department will review health statistics for any cities or towns for which elevated levels have been found.

Major Health Concerns

We have three major concerns regarding EDB:

1) EDB is a potent carcinogen in both sexes of different species and strains of test animals by all three routes of exposure---inhalation, ingestion and skin absorption. Cancers were found at multiple organ sites and, among some groups, as early as 10 weeks after the experiment had begun. Human epidemiological studies are inadequate to refute the assumption that EDB should be considered to have definite carcinogenic potential for humans.

2) EDB is a direct acting mutagen, and its metabolites, are, at times, even more mutagenic than EDB itself. The consistency of positive findings in such a wide spectrum of mutational tests, coupled with our understanding of the metabolism of EDB, is sufficient to presume that EDB is likely to pose a mutagenic hazard to humans.

3) EDB has been shown to adversely affect the reproductive systems of bulls, rats, and chickens. In humans, depressed sperm counts and abnormal forms have been reported in EDB-exposed workers.

Significance of Quantitative Risk Estimates

In reviewing the various models which have been used to quantify the carcinogenic risks associated with EDB, it is clear that lifetime exposure will yield unacceptably high risks at very low concentrations (low ppt range). The U.S. Environmental Protection Agency has clearly stated in official guidance that "there is a significant lifetime cancer risk for the general population even at the detection limit (0.02 ppb) for lifetime exposures". The risk estimates observed from the models are very useful as guidance in the decision-making process. However, given the large numerical uncertainties inherent in the quantitative risk assessment process, it would seem to us to be of equal if not greater importance to consider the total weight of the evidence in evaluating potential threats to human health. It should be stressed that the toxicological evidence that EDB may pose serious adverse effects is unequivocal. We, therefore, believe that exposure to EDB should be minimized or eliminated to the extent feasible.

The generally acceptable range of risks is usually quoted as falling between one in a hundred thousand to one in a million. We do not feel at all comfortable that communities may be subjected to a risk of excess cancer from drinking water alone of six in a hundred thousand. It should be pointed out, as the U.S. E.P.A. has also done in its emergency suspension order, that risks incurred from drinking water are in addition to those already present for food and ambient air. It is not clear to us why a short-term exposure of 100 ppt is recommended, since a) there does not seem to be any research which indicates that EDB disappears within a short period of time once it has appeared in a groundwater supply, and b) it is probable that exposure to EDB via a contaminated water supply may have already been occurring for some time.

We would suggest that if it is technologically and economically feasible to reduce exposure to EDB in water sooner than two years, this would be desirable.

Action by Other States

Finally, in looking at actions by other states, it appears that the limitation of the analytical capability rather than quantitative risk assessment has been the driving force in determining guidelines chosen. If it is feasible to undertake a sampling program at a detection limit of 0.02 ppb, then, according to EPA guidance, it would still be necessary to accept an increased lifetime cancer risk of 3 in 100,000. As indicated above, this is not within the generally acceptable range.

Conclusions and Recommendations

1. For levels at the detection limit and below (i.e. 0.02 ppb), it would not be reasonable to limit consumption. We think it would be a good idea to resample those wells which have shown traces of EDB to assure that these do not increase.
2. For EDB levels between 0.02 and 0.10 ppb, we believe that there is a small but definite risk to human health. This risk poses a long-term rather than an acute health hazard. Therefore, we are of the opinion that for wells within this range, the Department of Environmental Quality Engineering should evaluate on a case-by-case basis the feasibility, both technological and economic, of switching to an alternative water source. An implementation schedule which is as expeditious as feasible should be chosen, but we agree that in no case should this be longer than two years. We also agree with the importance of periodic monitoring both for confirmation and determination of possible trends.
3. We agree that if levels exceed 0.10 ppb, the water supply should be closed, provided the results have been confirmed and D.E.Q.E. has reason to believe that the elevated levels are likely to remain so.
4. This Department will review health statistics for any cities or town for which elevated levels have been found.

I hope that these comments will be of help to you. If we can be of further assistance, please let us know.

Sincerely,

BAILUS WALKER, JR., Ph.D., M.P.H.
Commissioner

BW/EK/bj

The Commonwealth of Massachusetts
Executive Office of Human Services
Department of Public Health
150 Tremont Street
Boston 02111

BAILUS WALKER, Jr, Ph.D, M.P.H.
Commissioner

A Summary of the Health Effects of Ethylene Dibromide

Prepared by:

Elaine Krueger, M.P.H.

Chief, Environmental Toxicology

Division of Environmental Health Assessment

February 1, 1984

A Summary of the Health Effects of Ethylene Dibromide

EDB is a clear, colorless, heavy, nonflammable liquid at room temperature. It has a characteristic mildly sweet odor detectable in air in the odor range of 10 ppm to 25 ppm. EDB is volatile and will escape into the air. It is soluble in ethanol and in water; 0.43 grams of EDB will dissolve in 100 g(100 milliliters) of water at 30°C. EDB does not degrade readily in soils over a two-week period, but will be mostly converted to ethylene and bromide by two months following application. Because of its solubility in water EDB has been detected in groundwater in some states. Baseline ambient air levels of EDB in 1976 for rural/suburban areas and metropolitan areas ranged from 0.05 to 0.10 and 0.1 to 0.4 micrograms per cubic meter, respectively. Downwind from citrus fumigation centers, EDB ambient air levels have been reported as high as 96 micrograms per cubic meter. Residues of EDB have been found in widely varying amounts in food following soil fumigation, fumigation of stored grain and spot fumigation of milling equipment.

MAJOR USES: EDB has been registered as a pesticide since 1948. The principal pesticide use, accounting for 90%, has been for preplant soil fumigation in which EDB is injected into the soil to protect a crop from attack by nematodes (root worms). EDB is also used in quarantine programs to fumigate citrus fruits and vegetables after harvest to prevent the spread of tropical fruit flies, and to fumigate stored grain and grain milling machinery to prevent insect infestation. Some minor uses include termite control, fumigation of storage vaults, beehives and timber.

EDB has been primarily used in the U.S. as a lead scavenger in leaded antiknock gasoline additives. Because of the Environmental Protection Agency's regulations which require a phase-out of leaded gasoline, this use of EDB has steadily dropped over the last few years and is expected to eventually become negligible. As this occurs, background levels of EDB in ambient air should also become negligible.

EXPOSURE FROM DIET: The U.S.EPA estimates that everyone in the U.S. is potentially exposed to significant levels of EDB in diet since EDB has been found in grain products, i.e. cereals and breads, and in citrus and tropical fruit which has been fumigated. The Agency's dietary risk assessment focused exclusively on wheat and wheat products since these comprise a large portion of the American diet. Therefore, there may be subpopulations who will experience a higher risk.

The Agency estimated that the typical American is exposed to a dietary EDB burden of 8.0 x10^{-5} mg/kg/day from the fumigation of stored wheat and 5.8x10-6 mg/kg/day for spot treatment of wheat milling equipment. The total is 8.6x10^{-5} mg/kg day. The increased lifetime risks of cancer from these exposures alone is estimated to be 1x10^{-4} or one excess case of cancer per 10,000 exposed persons.

ACUTE TOXICITY

EDB is easily absorbed by all three routes of exposure of ingestion, inhalation, and skin. Once in the body EDB is distributed by the blood to a variety of organs. EDB is rapidly metabolized. It has a biological half-life of about one day.

EDB, once metabolized, is converted to intermediates which may be even more toxic than EDB itself. EDB has a severe acute toxicity upon overexposure. Accidental death has been reported from absorption of less than 5 milliliters and also in workers who accidently spilled the substance onto their skin. Effects upon exposure may include eye, skin and respiratory system irritation which may become severe or painful upon overexposure. Damage to liver, kidney, spleen, caridovascular system and nervous system may also occur.

Acute toxicty is not the primary concern in exposure to EDB via diet.

CHRONIC TOXICITY

Carcinogencity in Animals: EDB has been found to be carcinogenic in rats and mice by all three routes of exposure-inhalation, ingestion and skin application. A National Cancer Institute biossay found squamous cell carcinomas of the stomach with metastases in 83 of 100 male rats and 70 of 100 female rats. None of this type of tumor was found in control animals. In 1979, EDB was demonstrated to be carcinogenic to mice by skin application. An increased incidence of skin and lung cancer was found.

The National Toxicology Program and the National Cancer Institute, in an experiment designed to simulate worker exposure, exposed rats and mice of each sex to EDB at levels above and below the current Occupational Safety

and Health Administration's Permissible Exposure Limit of 20 ppm. Animals were exposed for 6 hours per day, 5 days per week for 78-103 weeks. EDB was found to cause an increased incidence of nasal and pituitary gland cancer in males and females, and tumors of the circulatory and reproductive systems in males. In mice, increased incidence of lung cancer was seen in both males and females.

The National Institute for Occupational Safety and Health also conducted a chronic toxicity bioassay in rats and found an increased incidence of benign and malignant tumors of the spleen, mammary gland, and nasal cavity after inhalation exposure. It also found that with the addition of disulfiram, a drug in widespread use for the treatment of alcoholism, an approximate ten-fold increase in the incidence of liver cancer was found compared to exposure to EDB alone.

Few epidemiological studies are available concerning the health status of persons exposed to EDB. Those that are available are inadequate for assessing the carcinogenic risk to humans due to a number of limitations in study design and analysis, such as:the number of workers studied is too small; data on exposure levels is missing or incomplete; sufficient time has not elapsed since initial exposure to be able to see possible long term health effects.

Although definite conclusions canot be drawn as to whether EDB causes cancer in humans, it clearly can not be ruled out that EDB could be a human carcinogen. EDB is a potent carcinogen in both sexes of a number of different animal species and strains by all three routes of exposure. Carcinogenic responses were seen at multiple organ sites. The fact that EDB produces cancers at numerous sites in a number of species and strains by all three routes of administration serves to further strengthen the likelihood of it being a human carcinogen.

Mutagenicity: EDB has been found to be mutagenic in a wide spectrum of mutational test systems. This suggests that EDB may induce mutations in human populations, but it is not possible to quantitate relative risks for humans.
EDB is a direct- acting mutagen and its metabolites are also mutagenic, some even more so than EDB itself. It is likely that since EDB is a bifunctional alkylating agent, the most plausible basis for the induction of mutations is the covalent bonding of EDB to the genetic material.

Predicting the likelihood that a chemical may cause mutations in humans based on results in short-time mutagenicity assays is not as well-founded as predictions for other endpoints such as cancer. The consistency of positive findings in such a wide spectrum of mutational tests coupled with our understanding of the metabolism of EDB is sufficient to presume that EDB is likely to pose a mutagenic hazard to humans.

Reproductive Toxicity:

EDB has been shown to adversely affect the reproductive systems of bulls, rats and chickens. There is limited evidence that EDB may also exert adverse effects on human reproduction.

Bulls exposed to 2 mg/kg/day of EDB produced abnormal forms of spermatozoa, decreased sperm motility and count. When exposure was discontinued, recovery took place. Upon re-exposure and discontinuation again, recovery took longer to achieve.

Male rats treated with EDB at 10 mg/kg/day for 5 days and mated to untreated females produced decreased average live litter size.

In birds, the female reproductive system is affected by EDB exposure. A reduction in egg laying among hens was observed upon exposure to 10 mg/day for 2 months. Impaired fertility is also seen in hens. Male semen in birds does not seem to be effected by EDB.
In humans, depressed sperm counts and abnormal forms have been reported in EDB-exposed workers.

Animal studies clearly establish that the potential for human reproductive toxicity exists, particularly in the production of male sperm and the development of embryos. It is prudent to assume in the absence of adequate human data to the contrary, that humans are at least as sensitive as the most sensitive animal species.

CONCLUSIONS:

1. EDB is acutely toxic by all routes of exposure and is severely irritating upon contact with tissues.
2. Although EDB has a short biological half-life, some of its metabolites are more toxic than EDB itself.
3. EDB is an unequivocal carcinogen in animals and should, therefore, be considerred to have definite carcinogenic potential in humans. Human studies are inadequate to refute this assumption.

4. EDB itself and its metabolites are mutagenic in a number of different types of mutagenicity tests. This, plus consideration of the metabolism of EDB, supports the likelihood that EDB causes mutations in humans.
5. EDB causes severe reproductive disturbances in a number of animal species. A no effect level for the effects of EDB on reproduction in animals has not been established. There is some evidence, although not complete as yet, that EDB causes reproductive toxicity in humans.
6. Exposure to EDB should be minimized or eliminated to the extent feasible.

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